The Management of Condyloma Acuminata in the Pediatric Population

Donna A. Culton, MD, PhD; Dean S. Morrell, MD; and Craig N. Burkhart, MD
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CME EDUCATIONAL OBJECTIVES
1. Discuss the routes of transmission of condyloma acuminata in the pediatric population.
2. Determine which factors may suggest a route of transmission for condyloma acuminata in children other than sexual abuse.
3. Outline the available treatment options for condyloma acuminata in children.

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EDUCATIONAL OBJECTIVES OVERVIEW
In the primary care pediatrician’s office, patients present frequently with various dermatologic issues, ranging from very common, like warts, to those that are more uncommon. Even more common skin conditions can be difficult to treat, especially in the very young patient. However, various therapeutic options can be considered for the treatment of common skin conditions.

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The Management of Condyloma Acuminata in the Pediatric Population

Donna A. Culton, MD, PhD; Dean S. Morrell, MD; and Craig N. Burkhart, MD

Condyloma acuminata, more commonly known as genital warts, are caused by infection with human papillomavirus (HPV). Prevalence is increasing in adults, as well as in the pediatric population. Management of condyloma in the pediatric population can be difficult given the possibility of sexual abuse as a mode of transmission. Moreover, the available treatment options are only moderately efficacious and associated with significant rates of recurrence. Treatment can be quite painful, and multiple office visits are typically required. Finally, no large studies have been conducted in the pediatric population, and none of the medical treatments available is approved by the Food and Drug Administration (FDA) for use in children younger than 12 years. Each of these factors complicates management and treatment decisions in children with genital warts.

EPIDEMIOLOGY

Condyloma acuminata is quickly becoming the most frequently diagnosed sexually transmitted disease (STD) in the adult population, with 10% of adults having clinically evident lesions.1 Strikingly, more than half of sexually active women have been shown to harbor HPV virus, even in...
the absence of symptoms. Pediatric cases are also increasing, which is thought to reflect the increase in adult cases; however, little is known about the epidemiology of condyloma in the general pediatric population. Among children presenting to an STD clinic, 14.2% were diagnosed with condyloma, second only to syphilis (including congenital syphilis). Girls are more often affected than boys by a ratio of 3:1.

PATHOGENESIS

HPV is a non-enveloped, double-stranded DNA virus with more than 100 reported subtypes causing both clinical and subclinical infection of the skin and mucous membranes. Basal keratinocytes are the target cell infected and as cells become cornified, the virion is maintained. As these cornified cells are shed, so is the virion, thereby spreading potential disease-bearing particles into the environment, onto fomites, or onto the skin of another person.

Although not specific in their clinical manifestations, HPV types 6 and 11 are predominantly associated with genital warts, and HPV types 16 and 18 are more commonly associated with cervical neoplasias. Common warts (verruca vulgaris) are caused by many HPV types, but most often types 1-4. Although certain viral subtypes are typically associated with site-specific clinical presentations, overlap is common, especially in the pediatric population.

For example, a study of 29 cases of genital warts in girls younger than 5 years of age showed that 41% were due to HPV type 2, whereas only 3% of vulvar warts in adult women were caused by HPV type 2.

The incubation time following infection may last months; HPV can also remain in a latent phase. Therefore, the time from exposure to clinically evident lesions can range from months to years. The potential for unpredictable durations of latency make determination of the mode of transmission problematic.

CLINICAL PRESENTATION

Condyloma most often presents as 1- to 5-mm fleshy, skin-colored, verrucous-surfaced papules, which can coalesce into large plaques. They may be sessile or pedunculated and may even become quite exophytic forming cauliflower-like masses. They are typically asymptomatic, but may bleed or become painful or pruritic due to larger size or local trauma with toileting.

In prepubertal boys the most common site of involvement is the perianal area, while adult males often have lesions on the penile shaft. In girls, the perianal region and vulva are commonly involved.

MODES OF TRANSMISSION

In adults, sexual transmission is the most common route of inoculation. Although the possibility of sexual abuse must be considered for each individual case of condyloma occurring in a child, other routes of transmission should be considered as well, particularly in children younger than 4 years, a demographic where non-sexual transmission is more likely. Perinatal exposure may occur in utero via ascending HPV infection. In a study of HPV-infected pregnant women, 24 of 37 had detectable HPV genome in the amniotic fluid. Cases of congenital condyloma have been reported, further supporting ascending infection as a mode of transmission. Perinatal exposure can also occur as the neonate passes through the birth canal of an HPV-infected mother. Accordingly, the healthcare pro-
provider should attempt to elicit a maternal gynecologic history including any history of condyloma or abnormal pap smears. Another potential mode of transmission is auto- or heteroinoculation from non-genital warts of the child, parent, or other care provider.10,19,20 A thorough physical examination should be performed on any child with condyloma, inspecting for other non-genital warts, and parents should be questioned regarding personal history of verrucae as well. The long latency from exposure to clinical presentation must be considered, as exposure may precede development of condyloma by months to years.12,16 As mothers of pediatric HPV-infected patients may have subclinical cervical HPV infection (especially mothers of those who acquired HPV via in utero or perinatal exposure), physicians should advise potential carriers to seek medical attention from their primary care physician.

DIAGNOSIS

The diagnosis of condyloma is most often made clinically. Biopsy is rarely necessary, but histology shows typical hyperkeratosis and viral cytopathic change. HPV subtyping may be performed if clinical and histologic features are non-diagnostic but is not typically necessary.21 As site-specific subtypes are not as reliable in children as they are in adults, HPV subtyping has not been shown to be useful in making a case for or against sexual abuse as a mode of transmission.20,22

TREATMENT

Approximately 75% of untreated or treatment-resistant condyloma spontaneously resolve within months to a few years in children and adolescents with healthy immune systems.7,23,24 Therefore, active nonintervention is an option in children with asymptomatic lesions. However, studies suggest that lesions present for longer than 2 years are less likely to undergo spontaneous resolution.24 In these cases and in cases where the condyloma are symptomatic or affect function, treatment should be initiated. However, there are no FDA-approved treatments of genital warts in children younger than 12 years. Treatment of condyloma can be divided into surgical and non-surgical approaches. All surgical approaches rely on nonspecific tissue destruction. Many non-surgical approaches also utilize nonspecific tissue destruction, but treatments have expanded to include immunomodulatory agents as well. It is important to remember that no treatment has been shown to result in complete clearance of disease, that recurrences are common, and that multiple treatment modalities used in combination are often necessary to achieve significant improvement.25 In addition, many of the available treatments have not been studied in children, and in general no one treatment has been shown to be most efficacious. Therefore, treatment must be tailored to the individual patient.

Surgical Approaches

Cryotherapy in the form of liquid nitrogen is the most commonly utilized surgical approach to treatment. Complete clearance rates in adults range from 27%-100% but varies widely based on the experience of the surgeon.25,27 Johnson et al published a retrospective review of a single surgeon’s case series of 17 consecutive pediatric patients.28 Following one treatment, complete clearance was achieved in 16 patients with a recurrence rate of 23% at 1-year follow up. Only one patient (6%) had persistent disease. The authors argue that carbon dioxide laser ablation is safe, relatively atraumatic, and effective in the pediatric population. However, postoperative pain can be severe and general anesthesia is necessary. These factors should be taken into consideration.

Pulsed-dye laser is another alternative that has been shown to be effective in treating flat, plantar, and periungual warts.29 Treatment has been extended to genital warts in adults with one study showing complete resolution in all of 22 patients after an average of 1.59 (1-5) laser ses-
sions without evidence of scarring. In 13 patients, a single treatment was sufficient, whereas in the remaining nine patients up to five treatments were necessary with an average treatment interval of 14 to 21 days. Tuncel and colleagues found that treatment with pulsed-dye laser is also safe, effective, and well-tolerated in children. Postoperative pain and scarring are infrequent, making it an attractive option for children with condyloma.

Surgical excision is also an option for limited disease or single large lesions. Local or general anesthesia is required, and the procedure is usually performed in the office or outpatient surgical suite. In adults population, complete clearance rates range from 35% to 72% at 1-year follow up. If shave removal is performed, electrocautery to the base of the wound may add additional destruction of any remaining virally infected tissue. The use of this technique in children must be carefully considered given the need for general anesthesia.

Nonsurgical Approaches

Podophyllin is a resin that is derived from the rhizome of the *Podophyllum* species. The active agent of podophyllin resin is podophyllotoxin, which has antimitotic properties. Podophyllin is available as a 10% to 25% resin typically applied by the physician every 1 to 2 weeks until clearance is achieved. The resin should be washed off 4 hours after application to minimize local side effects such as redness and burning. In order to increase efficacy, the treatment is often combined with other destructive treatment options such as cryotherapy. Podophyllotoxin (podoflox) is available as a 0.5% solution or 0.15% cream and has increased purity and stability compared to podophyllin. It is applied by the patient or caretaker at home once or twice daily for several days per week as tolerated, and it is associated with slightly higher clearance rates in adults compared with podophyllin (56% to 79% compared with 41% to 47%). Moresi et al reported 15 of 17 children (88%) treated with podoflox experienced clearance of lesions over a duration of treatment ranging from 1 week to 4 months without significant side effects, suggesting that it is safe and effective for use in children.

Imiquimod 5% cream (Aldara) is a synthetic immune modulator that acts through the enhancement of both innate and cellular immune responses via extensive cytokine activation. It has been shown to be efficacious in treating external genital warts and is FDA-approved for use in children 12 and older. No large studies have been published on the safety and efficacy in children below 12 years of age, but case reports suggest that the compound is both safe and highly effective in the treatment of genital warts in children as young as 6 months, with clearance rates of 75%. Treatment typically involves application of imiquimod 5% cream overnight three times weekly with improvement within weeks to months. Side effects, which are usually mild and well-tolerated, include local pain, pruritus, and irritation. Because of the ease of application and the favorable side effect profile, imiquimod is quickly becoming first line treatment for condyloma in children.

Case reports of other topical agents have been reported. For example, cidofovir is an acyclic nucleoside phosphonate that acts as a DNA polymerase inhibitor. It is used primarily to treat cytomegalovirus retinitis in AIDS patients. Calisto et al reported improvement in condyloma of the glans penis in a 3-year-old boy using compounded topical cidofovir 1% cream applied daily for 5 consecutive days per week for 2 weeks. A second cycle was initiated after a 30-day pause and resulted in complete clearance without local or systemic side effects. There was no recurrence after 12 months.

Cimetidine is a histamine receptor antagonist that is often used to treat peptic ulcer disease. However, cimetidine also possesses immunomodulatory effects and has been reported to be useful in treating other conditions including verruca vulgaris. Although randomized controlled trials failed to show a significant benefit in non-genital warts in adults, Franco reported a case series of four children with condyloma treated with oral cimetidine. In two children, cimetidine was given as primary treatment, while in the other two children cimetidine was given to prevent recurrence. Dosing was initiated at 30 to 40 mg/kg/day divided into three doses and given for 3 months. All patients had complete clearance at 24-month follow-up. Cimetidine may be useful for primary and adjunctive therapy for condyloma in children, but more studies are needed.

CONCLUSION

When presented with a case of pediatric condyloma, a thorough physical examination and history (particularly of genital or non-genital warts in the mother or other care providers) must be performed. The American Academy of Pediatrics (AAP) recommends that all school-aged children presenting with condyloma for the first time should undergo a medical evaluation for child abuse including interview of the child and caretakers and testing for other sexually transmitted diseases. They also state that condyloma in children suggests sexual abuse if the lesions were not acquired perinatally. Regardless of the child’s age, sexual abuse must be considered in all children with condyloma. Given the difficulty in determining time of inoculation because of the long latency period, we advocate that in children younger than 4 years, non-sexual transmission is more likely and an alternative route of inoculation should be explored. When there is any concern by the parents or health care provider for sexual abuse, referral to an agency skilled in handling such cases should be made.
REFERENCES